A COMPARATIVE STUDY OF COMBINATION OF LOW DOSE KETAMINE AND MIDAZOLAM Vs KETAMINE AND MIDAZOLAM ALONE AS ORAL PREMEDICATION IN PEDIATRIC POPULATION

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CERTIFICATE

This is to certify that the dissertation entitled **"A Comparative Study of Combination of Low Dose Ketamine and Midazolam vs Ketamine and Midazolam alone as Oral Premedication in Pediatric Population"** is the bonafide record work done by Dr. LAKSHMI PRAKASH, submitted as partial fulfillment for the requirements of M.D. Degree Examinations – Branch X, Anesthesiology to be held in March 2007.

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AIM OF THE STUDY

The study aims to compare the effectiveness of oral low dose combination of Midazolam 0.25 mg/kg and Ketamine 3 mg/kg against conventional doses of Midazolam 0.5 mg/kg orally or Ketamine 6 mg/kg orally alone.

The study is intended to test whether there is any synergism in this combination and additional advantages in terms of time of onset, sedation, anxiety scores at parental separation, hemodynamic stability, recovery and postoperative side effects.

Introduction

Preparing the pediatric patients for surgery can be a complex process because of many individuals and factors involved. A hospitalized child has fear of separation, fear of pain, physical trauma and fear of stranger or unknown. The child can predict and anticipate pain on the basis of past experiences but cannot reason out or accept explanations from doctors and nurses. The child can't communicate the fear and anxiety but can only cry. The fear can be so severe that it can manifest as various forms of regressive behaviours after hospitalization.

Anxiety is created by the fear of the unknown and the uncertainity of what constitutes acceptable or appropriate behaviour in the hospital environment in elder children.

Hence traumatic experiences in the tender minds of children can be effectively prevented by a very good premedication. Parenteral premedication aggravates the fear and anxiety of pediatric patients. Oral premedication is an easily acceptable alternate route of achieving a calm, sedated child for smooth induction of anaesthesia. Oral premedication has good patient compliance and is very easy to administer. A calm child entering the operation theatre also provides parental satisfaction removing fears from their minds too.

Oral Ketamine and Oral Midazolam have been tried for the last twenty years as good premedicants with varying results. A combination of low dose Midazolam and Ketamine has been used in this study to find out whether there is advantage in terms of minimal side effects, sedation onset when compared to individual drugs.

PREMEDICATION IN PEDIATRICS

Premedicaton in pediatric age group is necessary for smooth induction of anaestheisa.

ADVANTAGES OF AN IDEAL ATRAUMATIC PREMEDICATION

An ideal atraumatic premedicant can decrease separation anxiety, improve induction by mask acceptance, minimizing emotional trauma. Decreased occurrence of negative behavioural problems post surgery has been observed. Kain , etal[1] have shown that premedication with Midazolam decreases the incidence of negative behavioural problems after surgery. They have also shown that increased preoperative anxiety can increase the incidence of postoperative negative behavioral problems.

ROUTES OF ADMINISTRATION OF PREMEDICATON

Premedication can be administered by various routes – nasal, oral, rectal, sublingual, parenteral – intramuscular and intravenous. Every route of administration has its own advantages and disadvantages. A successful premedication can be individualized according to the underlying medical conditions, length of the surgery, the desired induction of anaesthesia, and the psychological makeup of the child and the family. Although most of the routes are effective and reliable each has its own drawbacks.

Intramuscular Route is painful to administer, threatening to the child, can cause sterile abscess and is a major adverse experience – the child remembers the shot received.

Rectal medications make the patient feel uncomfortable cause defecation, occasionally burn. Irregular absorption of the drug is observed . Some degree of delayed respiratory depression is present.

Nasal medications can be irritating, though absorption is rapid. The drug may traverse directly into the central nervous system through the cribriform plate along the olfactory nerves. Only preservative free drugs can be given because of the potential for neurotoxicity. The drugs given in the nasal route are not completely retained in nasal mucosa especially in children but drip down into the pharyux and may be spit out by the children.

Intra venous route – need for intravenous cannulation – to be made painless by use of

EMLA..

Oral or sublingual route do not hurt but may have a slow onset or be spit out.

Hence Drug taste and patient cooperation are the main determinants of success.

ORAL PREMEDICATION IN PEDIATRICS.

Oral premedication is atraumatic, easy to administer and has good patient compliance. Various drugs have been tried for pediatric premedication. Before the advent of pediatric anaesthesia, sugar dipped pacifiers or whiskey nipples, were used in conjunctions with restraints for surgical operations such as pyloromyotomy in neonates.

DRUGS USED FOR ORAL PREMEDICATION

Earlier **oral chloral hydrate** 20 – 75 mg/kg was used. Peak effect reached in 1 hour in sedating the child.

Oral Midazolam 0.25 mg/kg - 0.5 mg/kg with onset within 20 minutes provides satisfactory sedation with minimal to no delay in recovery even for brief procedures. Main disadvantage of oral Midazolam is its bitter taste which is counteracted by combining with chocolate syrup or additives.

Oral Ketamine 3 – 10 mg/kg has been successfully used as a premedicant and results in a calm child within 15 minutes after premedication. Increasing doses increases side effects such as emesis.

Oral Ketamine 3 – 6 mg/kg with **oral Midazolam 0.25 mg/kg** –0.5 mg/kg has been found to provide profound depth of anaesthesia.

Fentanyl (10mcg/kg) Oral Transmucosal fentanyl Citrate provides an unique method of administration which takes advantage of rich absorption of drugs through the oral mucosa. But the disadvantages includes high costs and not available freely.

PHARMACOLOGY OF MIDAZOLAM

Midazolam, an imidazobenzodiazepine derivative is utilized as a premedicant, sedative and an aneasthetic induction agent. Synthesised in 1976 by Fryer and Walser, its unique structure confers a number of physicochemical properties that distinguish it from other benzodiazepine in terms of pharmacologic characteristics.

Midazolam (molecular weight 362) has a fused imidazole ring that is different from classic benzodiazepines. The imidazole ring accounts for the basicity , stability of an aqueous solution and rapid metabolism. pKa of Midazolam is 6.15 which permits preparation of salts which are water soluble. At physiologic pH, Midazolam becomes highly lipophilic and is one of the most lipid soluble benzodiazepines. The high lipophilicity accounts for its rapid absorption from gastro intestinal tract and rapid entry into brain tissue after intra venous administration.

PHARMACODYNAMICS

Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and antegrade amnesic effects.

Mechanism:

Facilitates inhibitory actions of GABA and mimics inhibitory actions of glycine .

EFFECTS ON CNS.

CEREBRAL EFFECTS – HYPOXIC BRAIN PROTECTION

Midazolam is a dose related manner, reduces cerebral metabolic rate for oxygen ($CMRO_2$) and cerebral blood flow and is helpful in cerebral protection against ischemic insult.

EFFECTS ON RESPIRATORY SYSTEM

Midazolam produces some respiratory depression decreasing the ventilatory response to carbondioxide. Apnea is related to the dose and also speed of injection. Apnea is more likely to occur in patients premedicated with opiods and receiving Midazolam.

EFFECTS ON CARDIO VASCULAR SYSTEM

In normal humans, significant reduction in systolic (5%) and diastolic (10%) blood pressure and increase in heart rate (18%) occurs. Cardiac index and left ventricular filling pressures are maintained but systemic vascular resistance may decrease 15-33%

METABOLISM AND PHARMACOKINETICS.

Metabolism involves hydroxylation of hepatic microsomal oxidative mechanism. The metabolites are excreted in the urine in the form of glucoronide conjugates. The elimination half life is 1.5 – 3.5 hours.

The high lipophilicity of Midazolam, coupled with its very high metabolic clearance and rapid rate of elimination cause it to have a short duration of activity.

After Oral administration, Midazolam is rapidly absorbed from gastro intestinal tract. Peak concentrations are achieved within one hour of ingestion. Because of extensive first pass metabolism only 40-50 percent of oral dose reaches systemic circulation. Hence Oral dose should be twice higher than intravenous dose to achieve comparable clinical effects.

USES OF MIDAZOLAM	DOSAGE	ROUTE
1. Induction of Anaesthesia	0.15.0.40mg/kg.	iv
2. Maintenance	Titration	iv
3. Premedication	0.07 – 0.10mg/kg	im
	0.25 – 0.5mg/kg	Oral
4. iv sedation	0.05 – 0.15 mg/kg	iv

Midazolam is preferred in maintenance of anaesthesia as it confers more amnesia, has fewer emergence complications. Midazolam is well suited for premedication as it has sedative and anxiolytic properties. Performance on tests of mental function returns to normal four hours after administration of Midazolam.

harmacology of Ketamine

Ketamine is a sedative, synthetic, nonbarbiturate compound which acts as CNS depressant producing rapid acting dissociative effect. It is a phencyclidine derivative described by Prof. Edward Domino as a potent psychedelic drug in 1970.

Ketamine is available as white crystalline powder which is diluted in water to yield a colorless solution containing 10/50/100mg/ml of racemic ketamine hyrochloride. Ketamine exists as – racemic mixture of R and S optical isomers with 'S' isomer having a potency 3-4 times that of 'R' isomer.

Ketamine produces dissociative anaesthesia, which is a trance like state in which the individual separates perception from sensation – a combination of profound analgesia and superficial sleep.

Mechanism of action

Ketamine is a noncompetitive antagonist of NMDA receptor Ca^{++} channel pore and also inhibits NMDA receptor activity by interaction with phyencyclidine binding site. It may also modulate opiod and muscarinic receptor activity.

routes of administration / doses

The intramuscular dose of Ketamine is 10mg/kg . Onset of action is 2 - 8minutes and the duration of action is 10 - 20 minutes. The intravascular drug dosage is 1.5 - 2 mg/kg administrated over a period of 60 seconds. Onset of action is within 30seconds and duration of action is 5-10 minutes. Infusion dose is 50mcg/kg/min. Oral dose of Ketamine is 3-10mg/kg . Ketamine can be given intrathecal and extradural route.

effects

Cardio Vascular System - Ketamine causes tachycardia, an increase in blood pressure, central venous pressure, cardiac output secondary to increase in sympathetic tone. Baroreceptor function is well maintained and dysrhythmias are uncommon.

Respiratory System – Ketamine causes mild stimulation of respiration with relative preservation of airway reflexes. Bronchodilation is the feature of action of the drug.

Central Nervous System – The state of dissociative anaesthesia is produced by Ketamine. The cerebral bloodflow, cerebral metabolic rate, intraocular pressure are increased. Amnesia occurs. Visceral pain is poorly obtunded by Ketamine. The EEG

demonstrates dominant theta activity and loss of alpha activity.

Gastro Intestinal Tract – Postoperative nausea and vomiting are common. Salivation is increased and no effect is observed in gastrointestinal motility.

Metabolic – The level of circulating adrenaline and noradrenaline are increased.

TOXICITY

Transient rashes occur in 15% of patients. Emergence delirium, unpleasant dreams, hallucinations are notable side effects.

Pharmacokinetics

Absorption – Ketamine is well absorbed after oral or intramuscular route. Oral bioavailability is 20%.

Distribution – Ketamine is 20-50%protein bound. Volume of distribution is 3l/kg. The distribution half life is 11min. Recovery is thus due to redistribution from brain to peripheral tissues.

Metabolism

Ketamine is converted in the liver by Ndemethylation and hydroxylation of the cyclohexyl amine ring. Some of the metabolites are pharmacologically active.

excretion

The conjugated metabolites are excreted in the urine. The clearance is 17ml/kg/min. and elimination half life is 2.5 hours.

The unpleasant dreams produced by Ketamine is reduced by premedication with a benzodiazepine. Ketamine reduces the requirement for inotropic support is septic patients.

USES

1. Ketamine is very useful as a premedicant and can be given orally, intramuscularly or intravenously before induction of anaesthesia.
2. Ketamine is used for induction of anaesthesia in poor risk patients with hypotension or asthma. It is the induction agent of choice in fallot's tetrology.
3. As a sole agent for short procedures like burns dressings and radiological and radiotherapy procedures is children.
4. As an agent for mass casualities in the field.
5. For pain relief in patients with chronic pain.
6. For analgesia both postoperatively and in patients receiving intensive care.

REVIEW OF LITERATURE

Midazolam:

Midazolam is currently the most popular premedicant in children. Several recent studies have focused attention in pH and composition when given in oral form. Commercial preparation of Midazolam was studied in a multicentered study by **Cote'etal** and was found to be effective in doses as low as 0.25 mg/kg. They also found that the Oral bio availability of the agent was 36% higher than anticipated and the onset time was 10-20 minutes in a majority of the patients.

Brosius and Bannister[14] measured the sedation scores (observer assessment of alertness/sedation) OAA/S as well as plasma levels of Midazolam in 50 healthy children 2-10 years old undergoing minor surgical procedures. The children received either commercially available Midazolam syrup (pH 2.4 to 3.6) or IV Midazolam mixed in syrpalta syrup (pH 4.5 to 5). They found lower sedation scores and higher plasma concentrations in patients receiving syrpalta syrup with Midazolam. The higher pH increases the oral absorption that decreases the first pass metabolism.

Several studies examining the long term effects of Midazolam prove lower incidence of negative postoperative behaviour in children **(Kain et al)**[17]**.**

Disadvantages of Larger doses of Midazolam

Viita nen et al and Valley et al demonstrated that recovery after sevoflurane anaesthesia was prolonged with larger doses of oral Midazolam.

On the other hand **Shimonaka and colleagues** found that they did not achieve adequate sedation with 0.5mg/kg or 1mg/kg of oral Midazolam in infants and children undergoing cardiovascular surgery. Their patients required 1.5mg/kg to achieve adequate sedation .

KETAMINE

Doses of 3 to 6 mg/kg per oral is effective as sedative and anxiolytic. However side effects like dysphoria, hallucinations were observed at higher doses by **Funk et al** [16]**.**

Recent studies have renewed interest in oral Ketamine, particularly when combined with oral Midazolam. **Trabold et al**[19] found that adding 3mg/kg of oral Ketamine to 0.5mg/kg of Oral Midazolam improved sedation at induction and did not prolong emergence or discharge from PACU.

Funk et al[16] compared oral Ketamine 3mg/kg added to oral Midazolam 0.5mg/kg with oral Ketamine 6mg/kg alone or oral Midazolam 0.5mg/kg alone.

They found separation, anxiolysis better with the combination of Ketamine and Midazolam than with either drug alone.

They surveyed the parents 1 to 7 days later and found the higher incidence of emesis or vertigo in patients who received only Ketamine. There were no occurrences of negative behaviour in any of the Groups.

The clinical practice guidelines for emergency department Ketamine dissociative sedation in children by **Steve M.Greene and Krauss**[9] states that " Preliminary evidence suggests that concurrent anticholinergics are unnecessary with Ketamine". Concurrent anticholinergics have been traditionally administered with the intent of minimizing Ketamine associated hypersalivation although recent evidences suggest that this recommendation has been overstated.

J. Cravero, G. Blike M.D., et al Dartmouth Hitchcock Medical Center in their pediatic sedation course have stated that oral secretions are mildly increased with oral Ketamine, athough administration of an antisialogogue is rarely required.

Comparison between Ketamine and Midazolam as oral premedicants in children by **Dr.Suranjith Debnath et al**[6] (Indian journal of Anaesthesia 2003, 47(1), 45-47) concludes that oral premedication with Ketamine 6mg/kg is better than Midazolam 0.5mg/kg in terms of better sedation scores, anxiolysis and smooth postoperative recovery.

Recommendation for using Ketamine as a sedative or analgesic or anesthetic during the peri-operative period by **Paul F white**[8] in 'Text of Intravenous Anesthesia" advices concurrent administration of a Benzodiazepine orally one hour before surgery and an Anti-sialogogue 5-10 minutes before induction.

In a study Comparing low dose versus high dose of Oral Midazolam and Oral Ketamine for pre-anesthetic medication in pediatric patients [Canadian journal of Anesthesia 50:A27 (2003)] has proved the onset of pre-operative sedation and recovery by Aldrete score was significantly early in the low dose group – Oral Ketamine 3mg/kg and Oral Midazolam 0.25mg/kg. Apart from delayed recovery, the high dose group – oral Ketamine 6 mg/kg and oral Midazolam 0.50mg/kg had higher incidence of salivation.

Epstein[30] anecdotally describes no difficulty with administration of Ketamine without an anticholinergic to approximately 1100 children. [Ref. Epstien FB, Ketamine Dissociative Sedation in Pediatric Emergency Medical Practice, American Journal of Emergency Medicine 1993, 11:180-182].

Materials and methods

Seventy five children aged between 1 and 12 years, ASA grade I, II undergoing elective surgery were included in the study. Consent obtained from their parents. The Hospital Ethical Committee approval obtained. The children were randomly allocated into 3 groups of 25 each. Oral atropine 0.02mg/kg was administered to all the children one hour before surgery.

Drugs used – Ketamine (50mg/mlvial), Midazolam (1mg/mlvial)

Group KM

Children of the group were given orally Ketamine in a dose of 3mg/kg and Midazolam in a dose of 0.25mg/kg after mixing with honey to avoid the bitter taste of the drugs, 30 minutes before surgery.

group k

Children of the group were given Ketamine in a dose of 6mg/kg Orally mixed with honey, 30 minutes before surgery.

group m

Children of the group were given Midazolam in a dose of 0.5mg/kg Orally mixed with honey, 30 minutes before surgery.

All the children were constantly monitored. The heart rate, Blood pressure,

Oxygen Saturation were recorded every 10 minutes upto 30 minutes before induction. Children were constantly observed for changes in the mood, behaviour, appearance, onset of sedation time when sedation score was less than or equal to 3. Sedation level at 30 minutes after premedication, anxiety level at the time of parental separation, at the time iv cannulation and mask acceptance was noted. The children were observed for side effects like hiccough, salivation, euphoria, nausea, vomiting preoperatively.

To assess the level of sedation, a 5 point sedation scale was used.

SCORE	SEDATION LEVEL
1	Barely arousable (full sleep)
2	Eyes closed (light sleep)
3	Eyes open but drowsy
4	Awake
5	Agitated

To assess the level of anxiety, a 4 point scale was followed.

SCORE	ANXIETY LEVEL
1	Calm, sleepy
2	Apprehensive but withdrawn from surroundings
3	crying
4	agitated, difficult to control

Intravenous Cannulation with appropriate iv cannula done. In crying, agitated children, halothane was administered by mask to calm the children and Nitrousoxide – oxygen - halothane by mask used to secure iv line. Isoyte P started at appropriate rate.

Intraoperative monitoring included precordial stethoscope, pulse oximetry, ECG, and noninvasive Blood pressure.

All the surgeries were proceeded under General Anaesthesia with controlled ventilation using Mapleson F circuit (Jackson Rees Circuit). Preoxygenation with 100% oxygen was carried out and anaesthesia induced with injection Thiopentone sodium 5 mg/kg iv and injection Succinylcholine 2mg/kg iv. Intubation done with appropriate endotracheal tube. Increased secretions during laryngoscopy and intubation if present were noted. Anaesthesia was maintained with Nitrous oxide 66% oxygen 33% and Halothane 0.5 - 1%. Injection vecuronium 0.08 mg/kg iv was used as muscle relaxant. At the end of the surgery, Injection Neostigmine 50mcg/kg iv and injection atropine 20 mcg/kg iv were used for reversal and patient extubated after recovery of reflexes.

Postoperatively Oxygen saturation, continuous heart rate monitoring done and Blood pressure recorded every 10 min. Recovery is assessed by Aldrete score. Crying, Irritability, nausea vomiting, hallucinations and any other side effects upto 6 hours were looked for in the postoperative period.

ALDRETE SCORE

PARAMETER	OBSERVATION	ALDRETE SCORE
1. Color	Pink	2
	Pale or dusky	1
	Cyanotic	0
2. Respiration	can breathe deeply and cough	2
	shallow but adequate exchange	1
	Apnea or obstruction	0
3. Circulation	BP within 20% of normal	2
	BP within 20-50% of normal	1
	BP deviating >50% from normal	0
4. Consciousnes	Awake, alert, oriented	2
	Arousable, but readily drifts back to sleep	1
	No movement	0
5. Activity	Moves all extremities	2
	Moves 2 extremities	1
	No movement	0

Post Anaesthetic Recovery score – Ideally the patient should be discharged when the Aldrete score or total score across the above parameters is 10.

OBSERVATION AND RESULTS

All the seventy five children accepted the drug and no vomiting was reported after swallowing the drug.

1.Onset of sedation

Onset of sedation was 9.92 ± 0.64 minutes in Group KM and 15.16 ± 3.80 minutes in Group K and 12.08 ± 3.83 minutes in Group M. Group KM has quick onset of sedation and is found to be statistically significant.

Group	Onset of sedation time in minutes
KM	9.92 ± 0.64
K	15.16 ± 3.8
M	12.08 ± 3.83

II. Sedation Score–

In Group KM

60% of patients were barely arousable (Sedation score - 1)

40% of patients had their eyes closed (Sedation score – 2)

Hence 100% of patients in Group KM attained a sedation score of < 3.

In Group K, 20% of patients had full sleep (sedation score – 1) 32% of patients had light sleep (score – 2), 36% of patients were drowsy (score 3) and 12% of the patients were awake.

In Group M, 20% of the patients had light sleep (score 2), 20% of the patients had their eyes open but were drowsy (score 3). But 60% of the patients were awake.

Hence 100% sedation was achieved in Group KM (score < 3) 88% of patients in Group K and 40% of patients in Group M were well sedated. The rest remained awake.

INFERENCE : Group KM had very good sedation score (100%) 60% of Group M patients remained awake.

Sedation Score	Group KM % of pts	Group K % of pts	Group M % of pts
1	60	20	0
2	40	32	20
3	0	36	20
4	0	12	60
5	0	0	0

III Anxiolysis Score

A. AT PARENTAL SEPARATION

92% of the patients **In Group KM** were calm and sleepy and 8% were apprehensive but withdrawn from surroundings.

In Group K 32% of the patients were calm and sleepy, 48% were apprehensive but withdrawn from surroundings and 20% were crying.

In Group M 16% of the patients were calm and sleepy, and 64% of the patients were apprehensive but withdrawn from surroundings and 20% of the patients were crying.

INFERENCE : Anxiolysis score was good in Group KM where 100% of the patients were calm at parental separation. Only 80% of the patients in group K and group M were calm at parental separation and the difference is significant.

Anxiolysis Score	Group Km % of pts	Group K % of pts	Group m % of pts
1	92	32	16
2	8	48	64
3	0	20	20
4	0	0	0

B. AT IV CANNULATION

ANXIOLYSIS SCORE AT IV CANNULATION

In Group KM, 88% of the patients were calm, and 12% of the patients were withdrawn from surroundings at iv cannulation.

In Group K, 44% of the patients remained calm,36% of the patients were apprehensive but withdrawn from surroundings, 12% were crying and 8% were difficult to control and were

noncooperative for iv cannulation.

In Group M, 12% of the patients remained calm, 16% were quiet withdrawn from surroundings, 60% were crying and 12% were difficult to control – were non co operative for iv cannulation.

INFERENCE : 100% of the patients in Group KM, 80% of the patients in Group K and 28% of patients in Group M remained calm at iv cannulation and the difference is significant.

None of the patient in Group KM cried at iv cannulation 12% of the patients in Group K and 60% of the patients in Group M cried at iv cannulation

Anxiolysis Score	Group KM % of pts	Group K % of pts	Group M % of pts
1	88	44	12
2	12	36	16
3	0	12	60
4	0	8	12

IV Recovery Time – Measured from Aldrete Score of 10

In Group KM, the recovery time was 36.92 ± 5.82 min and in Group K the recovery time was 29.0±8.72 min. and in Group M the recovery time was 18.24 ± 9.27 min and the difference is significant.

Group	Recovery Time in minutes
K M	36.92 ± 5.82
K	29.0 ± 8.72
M	18.24 ± 9.27

SIDE EFFECTS

Preoperatively 4% of the patients in Group KM had increased salivation, 12% of the patients in Group K had increased salivation.

60% of the patients were laughing and talking and could not be sedated in Group M. Difference is significant.

Preoperative Factors	Group KM %n of pts	Group K %n of pts	Group M %n of pts	Statistical data P = 0.05

Euphoria(Crying and laughing)	0	0	60	Difference is significant
Hiccough	0	0	8	Difference is Not significant
Increased salivation	4	12	0	Difference is Not significant

Postoperatively

52% of the patients cried postoperatively in Group M while none cried in the postoperative period in Group KM and Group K. 68% of the patients in Group M were irritable while none were irritable in group KM and Group K. The difference is significant.

16% of the patients in Group K had nausea and 8% had vomiting in Group K, while no nausea, vomiting was reported in Group KM and Group M postoperatively.

12% of the patients in Group K had hallucinations while no hallucination was reported in Group KM and Group K.

Postoperative Factors	Group KM % of pts	Group K % of pts	Group M % of pts	Statistical data P = 0.05
Crying	0	0	52	Difference is significant
Irritability	0	0	68	Difference is significant
Nausea	0	16	0	Difference is significant
Vomiting	0	8	0	Difference is not significant
Hallucination	0	12	0	Difference is significant

RESULTS SUMMARIZED

The onset time and post-operative time were statistically analyzed using student's unpaired 't' test.

The Sedation Scores, Anxiolysis Scores, pre-operative and post-operative side effects were analyzed with Chi-square test.

Parameter	Group KM % of pts	Group K %n of pts	Group M %n of pts	Statistical data P = 0.05
Onset of sedation time in minutes	9.92 ± 5.82	15.16 ± 3.80	12.08 ± 3.83	Difference is significant
Sedation score < 3 within 30 min.	100%	88%	40%	Difference is significant
Anxiolysis score:calm at parental separation	100%	80%	80%	Difference is significant
Anxiolysis score: cried at parental separation	0%	20%	20%	Difference is not significant
Anxiolysis score: calm at IV cannulation	100%	80%	28%	Difference is significant
Anxiolysis score: cried at IV cannulation	0%	12%	60%	Difference is significant
Anxiolysis score: non-cooperative at IV cannulation	0%	8%	12%	Difference is not significant
Post –operative recovery time in minutes	36.92 ± 5.82	29.0 ± 8.72	18.24 ± 9.27	Difference is significant

SUMMARY

A Study involving 75 children randomly allocated into 3 groups.

Group-KM Receiving low dose combination of Midazolam 0.25 mg/kg and Ketamine 3mg/kg orally mixed with honey, as pre-medication.

Group-K Receiving Ketamine 6mg/kg orally mixed with honey as pre-medication.

Group-M Receiving Midazolam 0.5mg/kg orally mixed with honey as pre-medication.

This pre-medication was given 15-30 minutes before surgery and evaluated.

The study proves that the combination of low dose Midazolam and Ketamine is efficacious in terms of providing.

i. Rapid onset of sedation

ii. Good sedation scores < 3 within 30 minutes with minimal side effects

iii. Better Anxiolysis scores at parental separation, IV Cannulation.

iv. Haemodynamic stability

v. Less incidence of post-operative complications

vi. Smooth induction

vii. Smooth Recovery post-operatively with no emergence reactions.

This has been supported by various studies and references by Trabold et al, Funk et al, Cote et al, Epstein FB.

DISCUSSION

Lin YC et al[11] showed that 6mg/kg of Ketamine made better sedation and anxiolysis than 0.5 mg/kg Midazolam.

Feld et al[8] and Alderson et al[9] observed that 0.5 mg/kg of Midazolam could not produce sleep in children even after 30 minutes.

The optimun dose of Midazolam as recommedded by Kothari et al[12] and Jone et al[17] for satisfactory sedation and anxiolysis is 0.75 mg/kg.

When Oral Midazolam 0.5mg/kg alone was used as a pre-medicant, only 40% of the patients included in the study achieved a sedation scored < 3 and 60% of the patients were euphoric 20% cried at parental separation, 60% cried at IV cannulation, 12% were non-cooperative. Post-operative crying and irritability were observed in more than 60% of the patients.

When oral Ketamine 6mg/kg alone was used as a pre-medicant, 88% of the patients included in the study achieved a sedation score < 3 and 80% were calm at parental separation and IV cannulation.

Although there was a 12% incidence of increased salivation, recovery was smooth except for occurrence of emesis (8%) proving that increasing the dosage of Ketamine is associated with increased dosage-related side effects [Ketamine-effects on Human performance and behaviour, Mozayani[4], Forensic Science Review – 14:123; 2002]

Many studies have proved that **combined oral Ketamine and Oral Midazolam** is better in terms of sedation, anxiolysis and smooth recovery.

Addition of Midazolam to Ketamine in low doses has proved that the combination has **synergistic** effect. The side effects of Ketamine like halluncination are nullified with Midazolam. Smooth recovery with stable haemodynamics is observed.

Studies by Funk[16] et al and Trabold[19] et al proved that the combination of Oral Ketamine 3 mg/kg and oral Midazolam 0.5mg/kg improved the depth of sedation and did not prolong emergence or discharge from PACU.

Oral pre-medication with a combination of low-dose Ketamine 3mg/kg and oral Midazolam 0.25mg/kg given 15-30 minutes before surgery has proved to be efficacious in terms of quicker onset (onset time 9.92 minutes) and better sedation score (100% sedated within 30 minutes; sedation score<3)

Minimal side effects were observed and incidence of salivation was less than 10% (Not significant).

Hemodynamic stability was well maintained and post operative recovery was quite and smooth without any side effects.

CONCLUSION

A combination of oral low dose Midazolam 0.25mg/kg and oral Ketamine 3mg/kg is found to be efficacious when compared to individual Midazolam 0.5mg/kg and individual Ketamine 6mg/kg in terms of better onset of sedation, adequate depth of sedation, anxiolysis Haemodynamic stability and good, smooth post-operative recovery.

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A COMPARATIVE STUDY OF THE EFFICACY OF ORAL LOW DOSE MIDAZOLAM AND KETAMINE COMBINATION Vs. ORAL MIDAZOLAM AND ORAL KETAMINE INDIVIDUALLY AS PREMEDICANTS IN CHILDREN

PROFORMA

Name	Age	Sex	IP NO.	Date	Time

Wt. (Kg)	
Ht. (Cm)	
Address-	

Pre-operative :

Premedication in Pediatrics

A COMPARATIVE STUDY OF THE EFFICACY OF ORAL LOW DOSE MIDAZOLAM AND KETAMINE COMBINATION Vs. ORAL MIDAZOLAM AND ORAL KETAMINE INDIVIDUALLY AS PREMEDICANTS IN CHILDREN

Sedation-Time of onset	Level of sedation at 30min.	Level of anxiety at parental separation	Level of anxiety at IV Cannulation	Mask Acceptance

Anesthetic Technique-

Post-Operative:

	SPO2	**Heart Rate**	**BP systolic mm/Hg**	**BP diastolic mm/Hg**

Parameter	**Observation**
Recovery	
Emergence	
Crying	
Irritability	
Hallucination	
Nausea	
Vomiting	

Side effects upto 6 hours post-operatively-

Prof &HOD

Theatre Anesthesiologist

Date

Dept of Anesthesia

Premedication in pediatrics